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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/692,077	10/19/2000	Kersten M. Small	13105	6315

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Holly D. Kozlowski
DINSMORE & SHOHL LLP
1900 Chemed Center
255 East Fifth Street
Cincinnati, OH 45202

EXAMINER	
JOHANNSEN, DIANA B	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 03/11/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/692,077	SMALL ET AL.	
	Examiner	Art Unit	
	Diana B. Johannsen	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-64* is/are pending in the application.

4a) Of the above claim(s) *23-29,45-62 and 64* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22, 30-44, and 63* is/are rejected.

7)☒ Claim(s) *12 and 21* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *0501; 0303*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restriction

1. Applicant's election with traverse of Group I, claims 1-22, 30-44, and 63, and of SEQ ID NO: 13, in the Response to Restriction Requirement filed December 3, 2003 is acknowledged. The traversal is on the ground(s) that "it would not be unduly burdensome for the Examiner" to examine all of the claims. This is not found persuasive. Applicant did not distinctly and specifically point out any supposed errors in the restriction requirement, or otherwise provide any reasons why Applicant believes it would not be unduly burdensome to examine all of the claims. As indicated in the Restriction Requirement of October 3, 2003, Inventions I-III are classified differently and require different fields of search, and therefore examination of these distinct inventions would in fact pose a serious burden. As Applicant has not provided any reasons why or evidence that such a burden is lacking, the restriction is proper for the reasons of record, and Applicant's arguments are not persuasive.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 23-29, 45-62, and 64, as well as SEQ ID Nos 14-22, are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the Response of December 3, 2003.

Information Disclosure Statement

3. Regarding the IDS filed May 8, 2001, it is noted that the examiner has inserted the correct patent number for the Dale et al patent, and added additional identifying

information for the last two "Other Documents" cited on page 4 of the Form 1449 provided by Applicant. It is requested that Applicant review and acknowledge the corrections made by the examiner.

Specification

4. The use of the trademarks GENBANK, QIAQUICK, WHATMAN, IMAGEQUANT, and PRIZM has been noted in this application. Trademarks should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks.

Claim Objections

5. Claims 12 and 21 objected to because of the following informalities: the claims refer to "random amplification DNA" rather than, e.g., "random amplification of DNA." Appropriate correction is required.

Drawings

6. The proposed drawing corrections and/or the proposed substitute sheets of drawings, filed on March 20, 2003, in which applicant has proposed correcting Figures 1-2, have been approved by the Examiner. A proper drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The correction to the drawings will not be held in abeyance.

7. It is noted that Figures 3-4 as filed on October 19, 2000 are also approved.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-22, 30-44, and 63 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-5 are indefinite because it is unclear as to whether the claims merely require detection of a polymorphic site, as indicated by the final step of claim 1, or whether the claims require that detection of a polymorphic site determines "alpha-2B-adrenergic receptor function," as recited in the preamble of claim 1. Further, the claims do not make clear how detection of a polymorphic site would allow one "to determine alpha-2B-adrenergic receptor function." Clarification is required.

Claims 1-5 are indefinite over the recitation of the limitation "the sample having a polynucleotide...." in claim 1 because there is insufficient antecedent basis for this limitation in the claims.

Claims 1-5 are indefinite over the recitation of the language "a polymorphic site comprising nucleotide positions 901-909 of SEQ ID NO: 1 or 2 or fragment or complement thereof" in claim 1. First, it is unclear as to what might constitute a site comprising particular "nucleotide positions" of a recited SEQ ID NO (as opposed to, e.g., a molecule comprising a particular fragment of a SEQ ID NO that is located at a particular position in that SEQ ID NO). For example, would the claims encompass any "polymorphic site" located at positions 901-909 of any molecule, or do the claims require

detection of a particular sequence of nucleotides located, e.g., in SEQ ID NO: 1 or SEQ ID NO: 2? Second, it is unclear whether the recitation "fragment or complement thereof" refers to a fragment or complement of the "polymorphic site" (and, if so, what might constitute a fragment or complement of a "site"), or whether this language is intended to refer to a polymorphic site that includes a "fragment or complement" of particular nucleotide positions, or of a particular sequence of nucleotides. Third, to the extent that the claims encompass polynucleotides that do not include either SEQ ID NO: 1 or SEQ ID NO: 2, it is not clear how the particular "nucleotide positions" required by the claims might be identified. Clarification is required.

Claim 3 is indefinite over the recitation of the language "wherein the polymorphic site is an insertion of 9 nucleotides at nucleotide position 901 to 909 of SEQ ID NO: 1." First, it is noted that the claim refers to 9 different nucleotide positions. It is unclear as to whether the claim is intended to require an insertion at each of these positions, a single insertion of 9 nucleotides within this regions, replacement of these 9 nucleotides with 9 different nucleotides, etc. Second, the language "polymorphic site is an insertion" is indefinite, as it is not clear whether this language in fact refers to a site at which an insertion may occur, or to a fragment or sequence that is inserted at a particular site. It is noted that a "polymorphic site" is a location within a molecule, not a molecule *per se*. Third, it is unclear as to whether the claim requires a polynucleotide comprising SEQ ID NO: 1, and if not, it is further unclear how "nucleotide position 901 to 909 of SEQ ID NO: 1" might be located or identified.

Claim 4 is indefinite over the recitation of the language "wherein the polymorphic site is a deletion of 9 nucleotides at nucleotide position 901 to 909 of SEQ ID NO: 1." First, , the language "polymorphic site is a deletion" is indefinite, as it is not clear whether this language in fact refers to a site at which a deletion may occur, or to a fragment or sequence that is deleted at a particular site. It is noted that a "polymorphic site" is a location within a molecule, not a molecule *per se*. Second, it is unclear as to whether the claim requires a polynucleotide comprising SEQ ID NO: 1, and if not, it is further unclear how "nucleotide position 901 to 909 of SEQ ID NO: 1" might be located or identified. The claim should be amended so as to make clear what must actually be detected in order to meet the requirements of the claim.

Claim 5 is indefinite over the recitation of the limitation "the complement of the polymorphic site comprises SEQ ID NO: 5 or 6." First, there is insufficient antecedent basis for this limitation in the claims. Second, as a "polymorphic site" is a location, rather than a molecule, it is unclear as to what would constitute a "complement" thereof.

Claims 6-12 are indefinite because it is unclear as to whether the claims are actually drawn to a method that results in "genotyping" as recited in the preamble of claim 6. Particularly, as the final step of claim 6 merely requires the detection of a "polymorphic site" within a molecule (rather than, e.g., a particular sequence located at a specific site that is characteristic of a particular genotype), it is unclear as to how the practice of the method steps of the claims would result in "genotyping."

Claims 6-12 are indefinite over the recitation of the language "a polymorphic site comprising nucleotide positions 901-909 of SEQ ID NO: 1 or 2 or fragment or

complement thereof" in claim 6. First, it is unclear as to what might constitute a site comprising particular "nucleotide positions" of a recited SEQ ID NO (as opposed to, e.g., a molecule comprising a particular fragment of a SEQ ID NO that is located at a particular position in that SEQ ID NO). For example, would the claims encompass any "polymorphic site" located at positions 901-909 of any molecule, or do the claims require detection of a particular sequence of nucleotides located, e.g., in SEQ ID NO: 1 or SEQ ID NO: 2? Second, it is unclear whether the recitation "fragment or complement thereof" refers to a fragment or complement of the "polymorphic site" (and, if so, what might constitute a fragment or complement of a "site"), or whether this language is intended to refer to a polymorphic site that includes a "fragment or complement" of particular nucleotide positions, or of a particular sequence of nucleotides. Third, to the extent that the claims encompass polynucleotides that do not include either SEQ ID NO: 1 or SEQ ID NO: 2, it is not clear how the particular "nucleotide positions" required by the claims might be identified. Clarification is required.

Claim 9 is indefinite over the recitation of the language "wherein the polymorphic site is an insertion of 9 nucleotides at nucleotide position 901 to 909 of SEQ ID NO: 1." First, it is noted that the claim refers to 9 different nucleotide positions. It is unclear as to whether the claim is intended to require an insertion at each of these positions, a single insertion of 9 nucleotides within this regions, replacement of these 9 nucleotides with 9 different nucleotides, etc. Second, the language "polymorphic site is an insertion" is indefinite, as it is not clear whether this language in fact refers to a site at which an insertion may occur, or to a fragment or sequence that is inserted at a particular site. It

is noted that a "polymorphic site" is a location within a molecule, not a molecule *per se*. Third, it is unclear as to whether the claim requires a polynucleotide comprising SEQ ID NO: 1, and if not, it is further unclear how "nucleotide position 901 to 909 of SEQ ID NO: 1" might be located or identified.

Claim 10 is indefinite over the recitation of the language "wherein the polymorphic site is a deletion of 9 nucleotides at nucleotide position 901 to 909 of SEQ ID NO: 1." First, , the language "polymorphic site is a deletion" is indefinite, as it is not clear whether this language in fact refers to a site at which a deletion may occur, or to a fragment or sequence that is deleted at a particular site. It is noted that a "polymorphic site" is a location within a molecule, not a molecule *per se*. Second, it is unclear as to whether the claim requires a polynucleotide comprising SEQ ID NO: 1, and if not, it is further unclear how "nucleotide position 901 to 909 of SEQ ID NO: 1" might be located or identified. The claim should be amended so as to make clear what must actually be detected in order to meet the requirements of the claim.

Claim 11 is indefinite over the recitation of the limitation "the complement of the polymorphic site comprises SEQ ID NO: 5 or 6." First, there is insufficient antecedent basis for this limitation in the claims. Second, as a "polymorphic site" is a location, rather than a molecule, it is unclear as to what would constitute a "complement" thereof.

Claims 13-15 are indefinite because it is unclear as to whether the claims are actually drawn to a method that results in "genotyping" a polynucleotide from a sample as recited in the preamble of claim 13. Particularly, the single step of claim 13 merely requires "performing a primer extension reaction" using an oligonucleotide; no reference

is made to the use of a sample, or to the achievement of "genotyping." Accordingly, it is unclear as to how or whether the practice of the method step of the claims would actually result in "genotyping."

Claims 13-15 are indefinite over the recitation of the language "an oligonucleotide comprising a nucleotide position 901-909 of SEQ ID NO: 1 or 2 or fragment or complement thereof" in claim 13. First, it is unclear as to what might constitute an oligonucleotide comprising a particular "nucleotide position" of a recited SEQ ID NO (as opposed to, e.g., a molecule comprising a particular fragment of a SEQ ID NO that is located at a particular position in that SEQ ID NO). For example, would the claims encompass any oligonucleotide including any of positions 901-909 of any molecule, or do the claims require detection of a particular sequence of nucleotides located, e.g., in SEQ ID NO: 1 or SEQ ID NO: 2? Second, it is unclear whether the recitation "fragment or complement thereof" refers to a fragment or complement of the oligonucleotide, or whether this language is intended to refer to an oligonucleotide that includes a "fragment or complement" of particular nucleotide positions, or of a particular sequence of nucleotides. Third, to the extent that the claims encompass oligonucleotides that do not include either SEQ ID NO: 1 or SEQ ID NO: 2, it is not clear how the particular "nucleotide position" required by the claims might be identified. Clarification is required.

Claim 14 is indefinite over the recitation of the language "wherein the oligonucleotide comprises a nucleotide sequence from about 10 to about 50 nucleotides." As an oligonucleotide by definition is itself composed of nucleotides, it is unclear as to how this language is intended to further limit the oligonucleotide of the

claim. Particularly, while the claim recites a length limitation on a "nucleotide sequence," the open transitional language "comprising" allows for the inclusion of additional oligonucleotide sequences (and therefore additional nucleotide sequences). Clarification is required.

Claims 16-22 are indefinite because it is unclear whether the claims are drawn to a "method of genotyping a polynucleotide" as recited in the preamble of claim 16, or to a method of obtaining "the genotype of an individual," as recited in the final process step. The claims should be amended so as to clarify whether the method is one of genotyping a polynucleotide or genotyping an individual.

Claims 16-22 are indefinite over the recitation of the limitation "the sample having a polynucleotide..." in step a of claim 16 because there is insufficient antecedent basis for this limitation in the claims.

Claims 16-22 are indefinite over the recitation of the limitation "the alpha-2B adrenergic receptor molecule comprising SEQ ID NO: 1 or 2 or fragment or complement thereof" in claim 16. First, there is insufficient antecedent basis for this limitation. Second, it is not clear whether the recitation "fragment or complement thereof" refers to a fragment or complement of the previously recited "polynucleotide," or whether this language indicates that fragments and complements of SEQ ID Nos 1 and 2 are considered to encode alpha-2B adrenergic receptor molecules, etc. Clarification is required.

Claims 16-22 are indefinite over the recitation of the limitation "the oligonucleotide" and "the incubation" in step b of claim 16 because there is insufficient

antecedent basis for these limitations in the claims. Regarding the recitation "the oligonucleotide," it is noted that while claim 16 previously refers to "at least one oligonucleotide," it does not recite or refer to a single, particular oligonucleotide.

Claims 16-22 are indefinite over the recitation of the limitation "the hybridization" in step c of claim 16 because there is insufficient antecedent basis for this limitation in the claims. While claim 16 does refer to the use of conditions that allow "specific hybridization" between molecules, the claim does not previous refer to hybridization occurring between the particular molecules employed in the claimed method. This rejection could be overcome by amending the claim to recite "permitting hybridization to occur."

Claims 16-22 are indefinite over the recitation of the phrase "identifying the polymorphic site to obtain the genotype of the individual" in claim 16, step d. It is unclear as to how the identification of a "polymorphic site" (as opposed to, e.g., the nucleotide or nucleotides present at such a site) would allow one to determine an individuals genotype. As all genotypes would be expected to contain the "polymorphic site" at which various nucleotides or sequences may be found, one of skill in the art would not expect to "obtain the genotype" of an individual by merely identifying a polymorphic site; rather, the identify of the nucleotide(s) located at the site would be required.

Claims 16-22 are indefinite over the recitation of the phrase "wherein the polymorphic site comprises an insertion or deletion of 9 nucleotides at nucleotide positions 901 to 909 of SEQ ID NO: 1 or 2" in claim 16. First, it is noted that the claim

refers to 9 different nucleotide positions. It is unclear as to whether the claim is intended to require an insertion at each of these positions, a single insertion or deletion of 9 nucleotides within this regions, replacement of these 9 nucleotides with 9 different nucleotides, etc. Second, the claim as written does not require either SEQ ID NO: 1 or SEQ ID NO: 2 (but rather may include only a "fragment or complement"), and it is unclear as to how the claimed method may be practiced in the absence of SEQ ID NO: 1 or 2.

Claim 17 is indefinite over the recitation of the phrase "amplifying the polymorphic site of the polynucleotide." It is unclear as to whether this language requires, e.g., amplification of a region of the polynucleotide that includes the polymorphic site, or whether the claim actually requires amplification of a "site" (as opposed to a molecule including the site). Clarification is required.

Claim 18 is indefinite over the inclusion of SEQ ID Nos 17-18 in the claim. It is noted that claim 16 requires an oligonucleotide "having a nucleotide sequence that is complementary to a region of the polynucleotide, and which, when hybridized to the region permits the identification of the nucleotide present at a polymorphic site of the polynucleotide." However, SEQ ID Nos 17-18 are identified in the specification as being primers that specifically hybridize to M13 vectors, not to a "polymorphic site" within the polynucleotide of the instant claims. Thus, it is unclear as to how or whether SEQ ID Nos 17-18 might function in the methods of the claims as presently written.

Claim 22 is indefinite over the recitation of the language "wherein the oligonucleotide comprises a nucleotide sequence from about 10 to about 50

nucleotides." As an oligonucleotide by definition is itself composed of nucleotides, it is unclear as to how this language is intended to further limit the oligonucleotide of the claim. Particularly, while the claim recites a length limitation on a "nucleotide sequence," the open transitional language "comprising" allows for the inclusion of additional oligonucleotide sequences (and therefore additional nucleotide sequences). Clarification is required. If the claim is intended to further limit the length of the oligonucleotide or of the "nucleotide sequence" recited in claim 16, the claim could be amended to recite, e.g., "wherein the oligonucleotide is from about 10 to about 50 nucleotides in length" or "wherein said nucleotide sequence is from about 10 to about 50 nucleotides in length."

Claim 30 is indefinite because it is unclear whether the claim is drawn to a "method of haplotyping" a gene, as recited in the preamble of the claim, or to a method of "determining the identity" of a polymorphic site, as recited in the final process step. The claims should be amended so as to clarify determination of the identity of polymorphic sites relates to haplotyping the recited gene.

Claim 30 is indefinite over the recitation of the phrase "a polymorphic site comprising nucleotide positions 901 to 909 of SEQ ID NO: 1 or 2 or fragment or complement thereof." First, it is not clear whether the claim encompasses a site comprising a "fragment or complement" of positions 901-909 of SEQ ID NO: 1 or 2, or whether the claim encompasses a polymorphic site comprising positions 901-909 of a "fragment or complement" of SEQ ID NO: 1 or 2. Second, to the extent that the claims encompass polynucleotides that do not include either SEQ ID NO: 1 or SEQ ID NO: 2, it

is not clear how the particular "nucleotide positions" required by the claims might be identified (e.g., how would one identify these particular positions in a "fragment or complement"?). Clarification is required.

Claim 30 is indefinite over the recitation of the language "determining the identity of an additional polymorphic site." It is not clear whether this language refers to determination or detection of a polymorphism or to determination of another "site" at which a polymorphism is known to be located, or whether the claim encompasses, e.g., identification of an additional site as being polymorphic. Clarification is required.

Claims 31-37 are indefinite over the recitation of the phrase "a polymorphic site comprising nucleotide positions 901 to 909 of SEQ ID NO: 1 or 2 or fragment or complement thereof which correlates to the disease." First, it is not clear whether the claim encompasses a site comprising a "fragment or complement" of positions 901-909 of SEQ ID NO: 1 or 2, or whether the claim encompasses a polymorphic site comprising positions 901-909 of a "fragment or complement" of SEQ ID NO: 1 or 2. Second, to the extent that the claims encompass polynucleotides that do not include either SEQ ID NO: 1 or SEQ ID NO: 2, it is not clear how the particular "nucleotide positions" required by the claims might be identified (e.g., how would one identify these particular positions in a "fragment or complement"?). Third, it is unclear as to whether the phrase "which correlates to the disease" refers back to the "polymorphic site," to "SEQ ID NO: 1 or 2 or fragment or complement thereof," to only the "fragment or complement," etc. Clarification is required.

Claim 34 is indefinite over the recitation of the language "wherein the polymorphic site is an insertion of 9 nucleotides at nucleotide position 901 to 909 of SEQ ID NO: 1." First, it is noted that the claim refers to 9 different nucleotide positions. It is unclear as to whether the claim is intended to require an insertion at each of these positions, a single insertion of 9 nucleotides within this regions, replacement of these 9 nucleotides with 9 different nucleotides, etc. Second, the language "polymorphic site is an insertion" is indefinite, as it is not clear whether this language in fact refers to a site at which an insertion may occur, or to a fragment or sequence that is inserted at a particular site. It is noted that a "polymorphic site" is a location within a molecule, not a molecule *per se*. Third, it is unclear as to whether the claim requires a polynucleotide comprising SEQ ID NO: 1, and if not, it is further unclear how "nucleotide position 901 to 909 of SEQ ID NO: 1" might be located or identified.

Claim 35 is indefinite over the recitation of the language "wherein the polymorphic site is a deletion of 9 nucleotides at nucleotide position 901 to 909 of SEQ ID NO: 1." First, the language "polymorphic site is a deletion" is indefinite, as it is not clear whether this language in fact refers to a site at which a deletion may occur, or to a fragment or sequence that is deleted at a particular site. It is noted that a "polymorphic site" is a location within a molecule, not a molecule *per se*. Second, it is unclear as to whether the claim requires a polynucleotide comprising SEQ ID NO: 1, and if not, it is further unclear how "nucleotide position 901 to 909 of SEQ ID NO: 1" might be located or identified. The claim should be amended so as to make clear what must actually be detected in order to meet the requirements of the claim.

Claim 36 is indefinite over the recitation of the limitation "the complement of the polymorphic site comprises SEQ ID NO: 5 or 6." First, there is insufficient antecedent basis for this limitation in the claims. Second, as a "polymorphic site" is a location, rather than a molecule, it is unclear as to what would constitute a "complement" thereof.

Claims 38-44 are indefinite over the recitation of the phrase "a polymorphic site comprising nucleotide positions 901 to 909 of SEQ ID NO: 1 or 2 or fragment or complement thereof which correlates to the disease, thereby diagnosing or prognosing the disease." First, it is not clear whether the claim encompasses a site comprising a "fragment or complement" of positions 901-909 of SEQ ID NO: 1 or 2, or whether the claim encompasses a polymorphic site comprising positions 901-909 of a "fragment or complement" of SEQ ID NO: 1 or 2. Second, to the extent that the claims encompass polynucleotides that do not include either SEQ ID NO: 1 or SEQ ID NO: 2, it is not clear how the particular "nucleotide positions" required by the claims might be identified (e.g., how would one identify these particular positions in a "fragment or complement"?). Third, it is unclear as to whether the phrase "which correlates to the disease" refers back to the "polymorphic site," to "SEQ ID NO: 1 or 2 or fragment or complement thereof," to only the "fragment or complement," etc. Finally, while it is clear that detection of a "polymorphic site" correlating to disease is diagnostic for the disease, this language does not make clear how detection relates to prognosis. Clarification is required.

Claim 41 is indefinite over the recitation of the language "wherein the polymorphic site is an insertion of 9 nucleotides at nucleotide position 901 to 909 of

SEQ ID NO: 1." First, it is noted that the claim refers to 9 different nucleotide positions. It is unclear as to whether the claim is intended to require an insertion at each of these positions, a single insertion of 9 nucleotides within this regions, replacement of these 9 nucleotides with 9 different nucleotides, etc. Second, the language "polymorphic site is an insertion" is indefinite, as it is not clear whether this language in fact refers to a site at which an insertion may occur, or to a fragment or sequence that is inserted at a particular site. It is noted that a "polymorphic site" is a location within a molecule, not a molecule *per se*. Third, it is unclear as to whether the claim requires a polynucleotide comprising SEQ ID NO: 1, and if not, it is further unclear how "nucleotide position 901 to 909 of SEQ ID NO: 1" might be located or identified.

Claim 42 is indefinite over the recitation of the language "wherein the polymorphic site is a deletion of 9 nucleotides at nucleotide position 901 to 909 of SEQ ID NO: 1." First, the language "polymorphic site is a deletion" is indefinite, as it is not clear whether this language in fact refers to a site at which a deletion may occur, or to a fragment or sequence that is deleted at a particular site. It is noted that a "polymorphic site" is a location within a molecule, not a molecule *per se*. Second, it is unclear as to whether the claim requires a polynucleotide comprising SEQ ID NO: 1, and if not, it is further unclear how "nucleotide position 901 to 909 of SEQ ID NO: 1" might be located or identified. The claim should be amended so as to make clear what must actually be detected in order to meet the requirements of the claim.

Claim 43 is indefinite over the recitation of the limitation "the complement of the polymorphic site comprises SEQ ID NO: 5 or 6." First, there is insufficient antecedent

basis for this limitation in the claims. Second, as a "polymorphic site" is a location, rather than a molecule, it is unclear as to what would constitute a "complement" thereof.

Claims 63 is indefinite because it is unclear as to whether the claim merely require "indirect" detection of a polymorphic site, as indicated by the final step, or whether the claim requires that detection of a polymorphic site determines "alpha-2B-adrenergic receptor function," as recited in the preamble. Further, the claim does not make clear how detection of a polymorphic site would allow one "to determine alpha-2B-adrenergic receptor function." Clarification is required.

Claim 63 is indefinite over the recitation of the limitation "the sample having a polynucleotide...." because there is insufficient antecedent basis for this limitation in the claim.

Claim 63 is indefinite over the recitation of the language "the polymorphic site comprising nucleotide positions 901-909 of SEQ ID NO: 1 or 2 or fragment or complement thereof." First, there is insufficient antecedent basis for this limitation in the claim. Second, it is unclear as to what might constitute a site comprising particular "nucleotide positions" of a recited SEQ ID NO (as opposed to, e.g., a molecule comprising a particular fragment of a SEQ ID NO that is located at a particular position in that SEQ ID NO). For example, would the claim encompass any "polymorphic site" located at positions 901-909 of any molecule, or do the claims require detection of a particular sequence of nucleotides located, e.g., in SEQ ID NO: 1 or SEQ ID NO: 2? Third, it is unclear whether the recitation "fragment or complement thereof" refers to a fragment or complement of the "polymorphic site" (and, if so, what might constitute a

fragment or complement of a "site"), or whether this language is intended to refer to a polymorphic site that includes a "fragment or complement" of particular nucleotide positions, or of a particular sequence of nucleotides. Finally, to the extent that the claims encompass polynucleotides that do not include either SEQ ID NO: 1 or SEQ ID NO: 2, it is not clear how the particular "nucleotide positions" required by the claim might be identified. Clarification is required.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

11. Claims 1-17, 19-22, 30-44, and 63 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Snapir et al (US 2001/0016338 A1 [published 8/2001; effective filing date 10/1999]).

Snapir et al disclose detection of a "common variant form (SEQ ID NO: 1) of the human α_{2B}-AR gene (SEQ ID NO: 3)," which variant gene "encodes a receptor protein (SEQ ID NO: 2) with a deletion of 3 glutamates, amino acids 307-309, from a glutamic acid (Glu) repeat element of 12 glutamates, amino acids 298-309, in an acidic stretch of 18 amino acids 294-311 (SEQ ID NO: 4), located in the 3rd intracellular loop of the receptor polypeptide" (see entire reference, particularly page 2 right column, paragraph

27). The deletion disclosed by Snapir et al constitutes a deletion of 9 nucleotides corresponding to nucleotides 901-909 of instant SEQ ID NO: 1 as compared to instant SEQ ID NO: 2, and is therefore encompassed by the instant claims. It is further noted that an inspection of SEQ ID NO: 1 of Snapir et al as compared to SEQ ID NO: 3 of Snapir et al reveals that Snapir et al's polymorphic site comprises instant "SEQ ID NO: 3 or 4 or complement thereof" and that "the complement of the polymorphic site comprises" instant "SEQ ID NO: 5 or 6." Additionally, it is an inherent property of the receptor taught by Snapir et al that it comprises instant "SEQ ID NO: 7 or 8 or fragment thereof."

With further regard to independent claims 6, 13, 16, and 30 and claims dependent therefrom, Snapir et al disclose both genotyping and haplotyping a cohort of Finnish men for the disclosed deletion genotype (see entire reference, particularly page 2, paragraphs 26-28, and the entire "Experimental Section" spanning pages 3-5). With particular regard to claims 12, 13-17, 19-22, and 63, Snapir et al disclose a variety of direct and indirect methods that may be employed in detecting their variant, including sequencing, PCR (which itself requires primer extension), SSCP, DGGE, RFLP, "gene chip technology," allele specific hybridization, etc. (see page 3, paragraphs 32-33). With further regard to claim 22, it is noted that the primers employed by Snapir et al meet the length requirements of the claim (see, e.g., page 3, paragraph 40 and page 4, paragraph 44). With respect to claims 31 and 38 and claims dependent therefrom, Snapir et al disclose the use of their method in screening for and diagnosing a

cardiovascular disease, particularly "vascular contraction of coronary arteries" (see page 1, paragraphs 7 and 12-14, and page 2, paragraphs 15-20, 23, and 28).

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Snapir et al (US 2001/0016338 A1 [published 8/2001; effective filing date 10/1999]) in view of Baldwin et al (American Journal of Hypertension 12:853-857 [9/1999]) and Newton ("Chapter 6: Primers," in *PCR Essential Data*, C.R. Newton, ed., John Wiley & Sons, Chichester, 1995, pages 49-56).

Snapir et al disclose detection of a "common variant form (SEQ ID NO: 1) of the human α_{2B}-AR gene (SEQ ID NO: 3)," which variant gene "encodes a receptor protein

(SEQ ID NO: 2) with a deletion of 3 glutamates, amino acids 307-309, from a glutamic acid (Glu) repeat element of 12 glutamates, amino acids 298-309, in an acidic stretch of 18 amino acids 294-311 (SEQ ID NO: 4), located in the 3rd intracellular loop of the receptor polypeptide" (see entire reference, particularly page 2 right column, paragraph 27). The deletion disclosed by Snapir et al constitutes a deletion of 9 nucleotides corresponding to nucleotides 901-909 of instant SEQ ID NO: 1 as compared to instant SEQ ID NO: 2, and is therefore encompassed by the instant claim. However, while Snapir et al disclose detection of their variant by PCR amplification (see page 3-4, paragraphs 40-46), Snapir et al do not disclose the use of a primer consisting of SEQ ID NO: 13 or the complement thereof. Baldwin et al disclose a method of detecting polymorphisms in the human α_{2B}-AR gene in which overlapping fragments of the gene are sequenced, and in which the same variant sequence disclosed by Snapir et al is detected (see entire reference, particularly page 854, right column-page 855, left column; and Table 1). The primers employed by Baldwin et al in sequencing include primer 1311 (see Table 1); nucleotides 1-19 of primer 1311 are the reverse complement of nucleotides 1-19 of instant SEQ ID NO: 13. Accordingly, instant SEQ ID NO: 13 targets the same region of the human α_{2B}-AR gene sequence as the primer of Baldwin et al, but in the reverse orientation. Baldwin et al further disclose that primer 1311 hybridizes at nucleotide 619 of the human α_{2B}-AR gene, and thus is located 5' of the polymorphism taught by both Baldwin et al and Snapir et al. Newton et al teach the design of primers for PCR, providing guidance with respect to desirable characteristics

as well as properties to avoid when designing PCR primer pairs (see entire reference, particularly pages 50-51).

In view of the teachings of Baldwin et al, and given the guidance provided by Newton regarding the design of PCR primers, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Snapir et al so as to have employed therein a variety of different primers, including a primer consisting of instant SEQ ID NO: 13. Newton discloses that runs of single bases are undesirable in PCR primers, and the sense primer employed by Snapir et al in genotyping includes such a run (a run of 4 guanines; see paragraph 44, page 4, sequence of SEQ ID NO: 9)(see page 51 of Newton). Accordingly, one of skill in the art would have been motivated to have modified the sense primer employed by Snapir et al so as to have prepared one or more alternative primers conforming with the principles of primer design taught by Newton for the advantage of preparing primers usable in Snapir et al's method that could be employed more easily and readily in a variety of amplification conditions. As Baldwin et al disclose that the region of their primer 1311/instant SEQ ID NO: 13 may be successfully targeted in PCR amplification, an ordinary artisan would have been motivated to have selected primers that hybridize specifically to this region (including a primer consisting of SEQ ID NO: 13), rather than to have experimented to identify other regions suitable for primer hybridization, for the advantages of convenience and efficiency in practicing the method suggested by Snapir et al. Absent a showing of unexpected results with the particular sequence of the claim, any primers targeting the region suggested by Baldwin et al and meeting the criteria of

Newton would be obvious over Snapir et al in view of Baldwin et al and Newton. It is further noted that as SEQ ID NO: 13 meets the desired criteria disclosed by Newton for length, melting temperature, GC content, etc., an ordinary artisan would have had a reasonable expectation of success in employing this primer, as well as a variety of other primers suggested by the references, in the method of Snapir et al.

Conclusion

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana B. Johannsen whose telephone number is 571/272-0744. The examiner can normally be reached on Monday-Friday, 7:30 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached at 571/272-0745. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Diana B. Johannsen
Patent Examiner
March 5, 2004